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A will and a way to fund medicines for rare diseases: the story of human growth hormone replacement for adults with growth hormone deficiency

Abstract

Growth hormone replacement therapy was recently recommended by the Australian Pharmaceutical Benefits Advisory Committee (PBAC) for listing on the Pharmaceutical Benefits Scheme (PBS) for adults with severe growth hormone deficiency and impaired quality of life. This approval was significant for two reasons. First, the application was spearheaded not by the pharmaceutical industry, but rather by health professional bodies, which appointed a working group to prepare a “public interest” submission to PBAC. Second, the recommendation to subsidise growth hormone came on the back of two previous industry-sponsored applications, both of which had failed on the basis of uncertainty about efficacy and cost effectiveness. There are important lessons to learn from this process about the power of professional groups to drive health policy and attain funding for rare diseases.

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In Australia, decisions about which medicines to approve for marketing are made by the Therapeutic Goods Administration (TGA). Once a medicine has been approved for marketing, it might be subsidised by government, hospitals, private insurers, or pharmaceutical companies. At the Federal level, recommendations about funding medicines are made by the Pharmaceutical Benefits Advisory Committee (PBAC), an independent

statutory body that makes recommendations to the Minister for Health about which medicines should and should not be subsidised on the Pharmaceutical Benefits Scheme (PBS). If PBAC makes a positive recommendation, the government decides whether or not to fund the medicine and prices are then negotiated by the Pharmaceutical Benefits Pricing Authority (PBPA). If PBAC makes a negative recommendation, medicines are not subsidised and, unless an alternative source of funding can be found, such as hospital or industry compassionate access, patients are left to pay for these medicines themselves. Until recently, this was the situation for adult patients with growth hormone deficiency (GHD) resulting from congenital or acquired pituitary failure, who were not able to access publicly subsidised growth hormone replacement.

Recombinant human growth hormone (GH), also known as somatropin, has long been PBS listed for growth hormone deficiency and other causes of significant short stature in children. The use of somatropin in adults with severe GHD has been approved by the Therapeutic Goods Administration. It is also recommended by health professional organisations internationally, and has been reimbursed in many countries with advanced health systems (e.g. United Kingdom (UK), Sweden, Germany, New Zealand) for many years.¹⁻³ Nonetheless, PBAC twice recommended (in 2001 and 2011) against listing somatropin on the PBS for adults with severe GHD on the basis of uncertainty about the quality of the evidence regarding safety, efficacy and cost-effectiveness of subsidised treatment.⁴ As a consequence, adult patients with GHD incur the full cost of \$5,000 to \$10,000 per annum for GH replacement.

This is significant because growth hormone is a major metabolic hormone controlling the structural and functional integrity of all body tissues and organs. Deficiency of GH in adulthood results in obesity, insulin resistance, loss of muscle and bone mass, and impaired physical and psychological function. These problems collectively diminish quality of life by causing, among other symptoms, mood fluctuations, anxiety, depression, loss of vitality, fatigue and lack of strength. This, in turn, has an impact upon working capacity, life satisfaction, and productivity.^{1 5-7}

Following the 2011 PBAC rejection, the Endocrine Society of Australia (ESA) and the Australasian Paediatric Endocrine Group (APEG)—the two professional bodies representing Australian Endocrinologists—reviewed PBAC’s Public Summary Document to understand why there would have been uncertainty around the benefits of GH replacement. It was clear that evidence presented to PBAC had been heterogeneous, comprising a spectrum of patients with mixed aetiologies and varying degrees of GH deficiency, in whom different outcomes were quantified in different studies. In particular, inclusion of patients without severe GHD in previous studies reduced the potential to show a benefit from GH replacement. This motivated ESA/APEG to create a working group in 2012 to undertake a critical review of the literature presented to PBAC, to examine any new evidence, and to conduct a feasibility assessment for a submission to PBAC.

There was no new randomised-controlled trial evidence to analyse (indeed, no new randomised clinical trials had been conducted over the previous 10 years, which is not surprising given that somatropin is now subsidised in most western countries). The only important new data that had emerged since the 2011 PBAC submission was an

observational study from New Zealand reporting the efficacy of somatropin since it had been approved by PHARMAC (New Zealand's equivalent to PBAC).⁸

The working group therefore began by commissioning a researcher (WL) (paid by the two professional societies) to conduct a reanalysis of the trials that had been presented to PBAC. This analysis included all relevant studies, including those that demonstrated a neutral or negative effect on the parameters of interest. Studies were excluded only if they did not represent the population for whom subsidy was being sought (i.e. patients with severe GH deficiency) or if they used unvalidated diagnostic tests that would have likely included patients without GH deficiency (two of which has been presented previously to PBAC^{9 10}). This reanalysis (available on request) provided persuasive evidence supporting the feasibility for a resubmission to the PBAC. Table 1 summarises the evidence-based biochemical, physiological and clinical benefits of GH replacement therapy in GH deficient adults.

Table 1 about here

As this was the first time that the ESA and APEG had undertaken a PBAC submission, the working group consulted the Department of Health, who provided encouragement and advice. The Department also stated their willingness to consider the application as a "public interest" submission for which the application fee of \$250 000 would be waived (a public interest submission is one that is likely to benefit a population, but would be financially unviable if the application fee needs to be paid). The Department advised the group that research demonstrating positive effects on QoL would be considered seriously, and also

suggested alternative approaches, such as using surrogate markers, provided that economic modelling could demonstrate the likelihood of “hard” clinical outcomes.

The results of the preliminary analysis were presented to all five Australian manufacturers of somatropin, who agreed to provide financial support for a joint ESA/APEG-led submission to PBAC. The companies each contributed an equal sum of money to commission a health technology consulting company (Optum) to conduct a more detailed analysis of the evidence and prepare an application to PBAC, but had no further involvement in the application process.

In 2016, on behalf of the working group, Optum submitted an application to PBAC, which was predominantly modelled on the New Zealand scheme for GH replacement in adults. The application was considered at the November 2016 meeting, at which PBAC deferred its decision in order “to seek further comparative analysis on the range of clinical benefits provided by somatropin, to clarify the proposed PBS restriction, and to allow the Department to discuss appropriate pricing in this setting with sponsors of somatropin products registered for use in adults.”¹¹ A refined submission was reconsidered at the July 2017 meeting, and a positive recommendation was officially recorded in August 2017.¹² A number of processes are currently underway prior to final listing, including negotiation of a price followed by further financial modelling to assess likely utilisation and financial impact, and agreement on restrictions.

Practical lessons and reflections

The process that the ESA/APEG working group undertook was protracted and was made difficult by a lack of specific guidance about how to prepare PBS submissions in the public interest. Nevertheless, the eventual positive recommendation demonstrates that it is possible for health professional groups (including those without substantial financial resources) to initiate and lead successful submissions for listing of medicines on the PBS. Given the complexity of a submission to PBAC, which requires detailed economic modelling, this may require collaboration with pharmaceutical companies—who in this instance joined forces in the public interest.

The process also demonstrates that the Department of Health is willing and able to provide strategic guidance to groups who might wish to prepare public interest submissions, and to take a flexible but reasoned approach to the assessment of evidence about treatments for rare diseases—a process that can be both methodologically and morally complex.¹³ In this regard, it is noteworthy that, while expressing reservations about some of the data presented, PBAC recognised that the level of evidence that could be obtained was limited by the rarity of GHD, coupled with the need for daily injections (which makes people less willing to participate in long-term placebo-controlled trials). Indeed, a significant weight of the evidence presented to PBAC was provided from long-term open-label studies, most notably a 3-year observational study from New Zealand.⁸

It is also noteworthy that, while consumers were not directly involved in the working group's activities, PBAC stated in its Public Summary Document that it had taken account of clinical and consumer input and had found this helpful in making their recommendation. They made note of input from individual patients, carers and clinicians, from the Australian

Pituitary Foundation (which presented the results of a survey of its members) and from international consumer advocacy organisations.¹¹

This is not the first time that professional groups have taken the lead to influence PBS listing of medicines. In 2013, the Australian College of HIV Medicine successfully lobbied for removal of haematological restrictions to initiate therapy for human immunodeficiency virus.¹⁴ In contrast, in 2007, the Influenza Specialist Group was unsuccessful in an attempt to list influenza vaccine for adults aged 50-65.¹⁵ Given the broad clinical experience of such professional bodies, we propose there should be a pathway to facilitate their greater influence on medication availability in Australia.

Within endocrinology, there are treatments of other rare diseases that are not even registered for use with the Therapeutic Goods Administration despite the fact that they are clearly recommended in international clinical practice guidelines. Two examples are ketoconazole and metyrapone for Cushing's disease.¹⁶ This demonstrates that, in the Australian system, medications may not even be registered if there is not a financial motivation to do so, and that professional groups might need to intervene in the process of registration as well as subsidisation.

In summary, the positive outcome for the approximately 1000¹ patients in Australia with severe GH deficiency and poor QoL suggests that PBAC and the Department of Health will support professional groups who wish to advocate for PBS listing of medications in the public interest. We report on the process that we undertook as a potential roadmap for other professional bodies hoping to facilitate access to therapies for their patients.

1. The 1000 estimate is based on the prevalence of GHD in the population and the proportion of these patients with severe GH deficiency AND impaired QoL within this population. The prevalence of hypopituitarism is derived from data in the UK¹⁷ and Spain,¹⁸ of 200 – 375 per million. The number of adults with GHD of varying severity in Australia is thus estimated at 6500-7500. GHD is diagnosed by a peak GH of < 5 ng/mL to the insulin tolerance test, 50% of whom have severe GHD (< 2.5 ng/mL) Within this subgroup, those in the highest tertile of QoL impairment are eligible for GH replacement. Thus, about 15% (one third of 50%) the population with GHD (approximately 975 – 1125), qualify for reimbursement under the PBS. These numbers are proportionately similar to the 191 patients who entered the GH treatment program in New Zealand⁸ which has a population of 4.5 million.

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Table 1: Benefits of GH replacement therapy in adults with GH Deficiency

	Benefits
Body composition	Reduction in fat mass
	Increase in muscle mass
	Increase in bone mass
Metabolism	Increase in resting energy expenditure
	Increase in fat oxidation
	Stimulation of protein anabolism
Physical Function	Increase in cardiac function
	Increase in exercise capacity
	Increase in muscle strength
Cardiovascular risk	Reduction in LDL cholesterol
	Reduction in inflammatory risk markers
	Increase in endothelial function
Mood	Improvement
Quality of life	Improvement

